Visualizing the Impact of Chemical Substructures on Compound Activity for Improving the Drug Discovery Process

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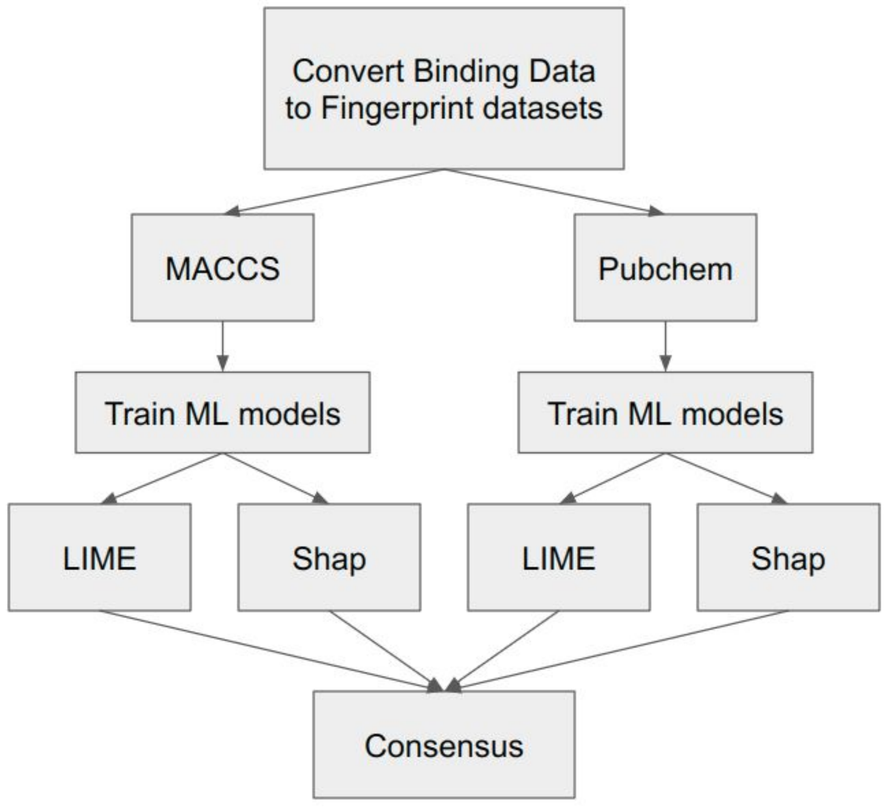
Abstract

- Machine learning (ML) can be a powerful tool in drug discovery but often operates as a “black box”
- Interpretation techniques exist which can provide insight in *why* the ML model predicts certain things
- This concept was applied to a drug-discovery context using Sibila, where interpretation of the ML models can indicate which substructures can be beneficial for compound activity

Interpretation Methods

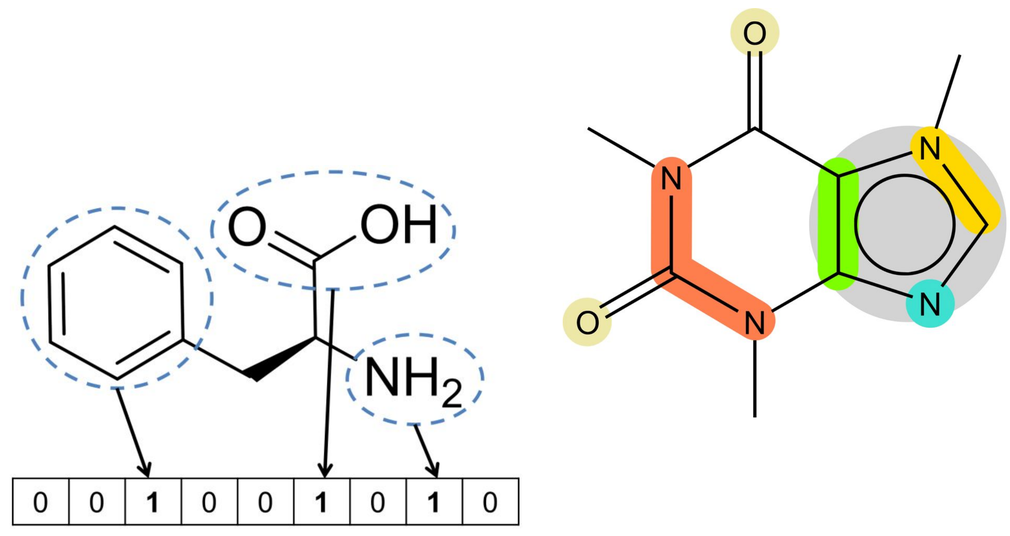
- LIME
- Shap
- …
- Different ways of identifying important features → combine to get a better picture
- Train and interpret models using Sibila

Workflow



Fingerprints

- MACCS keys (166 features)
- Pubchem Fingerprint (881 features)
- If feature substructure is present:
  → feature bit is set to 1, else to 0



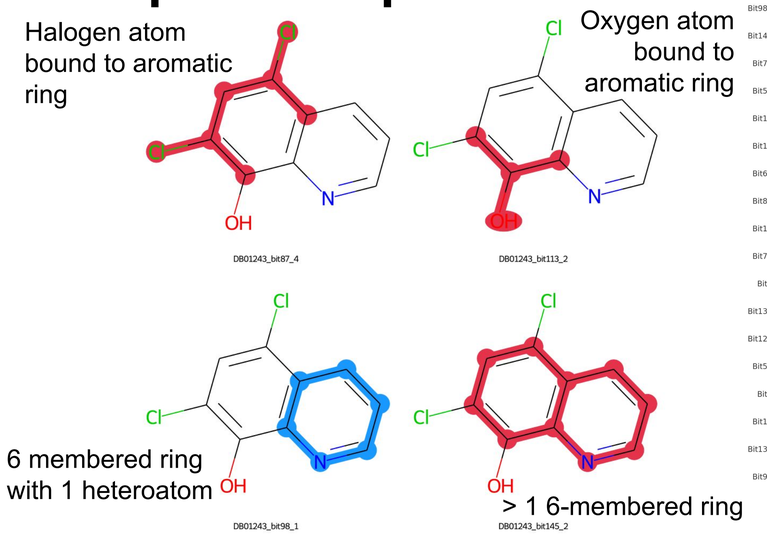
Output example from ANN

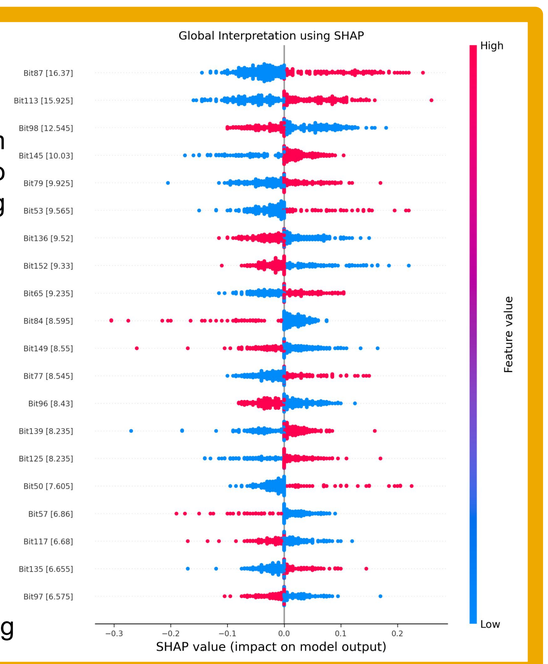
Halogen atom bound to aromatic ring

Oxygen atom bound to aromatic ring

6 membered ring with 1 heteroatom

> 1 6-membered ring





Conclusions

- ML-based Virtual Screening is powerful in drug discovery
- Interpretation techniques combined with substructure fingerprints aid in model interpretation
- Consensus of interpretation results from different fingerprints and models provides robust insights
- Sibila facilitates training and interpretation of models

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NLHPC National Laboratory for High Performance Computing Chile

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